General

Guideline Title

Optimal systemic therapy for early female breast cancer.

Bibliographic Source(s)

Eisen A, Fletcher GG, Gandhi S, Mates M, Freedman OC, Dent SF, Trudeau ME, Members of the Early Breast Cancer Systemic Therapy Consensus Panel. Optimal systemic therapy for early female breast cancer. Toronto (ON): Cancer Care Ontario (CCO); 2014 Sep 30. 232 p. (Program in Evidence-Based Care Evidence-Based Series; no. 1-21). [473 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario (CCO) Web site for details on any new evidence that has emerged and implications to the guidelines.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Recommendations and Key Evidence

The most recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview confirms the benefit of adjuvant chemotherapy vs none in improving outcomes in early breast cancer. The EBCTCG found similar relative benefit for all subgroups, although the absolute magnitude of benefit depended on baseline risk.

In all recommendations it is assumed that patient preference is considered and that final treatment is determined in consultation between the patient and the doctor. This is mentioned more explicitly in a few recommendations in which the balance between risk and benefit is less clear overall or for certain patient groups.

Recommendations 1-7. Patient/Disease Characteristics and Recurrence Risk

Recommendations for adjuvant systemic therapy in breast cancer are mostly guided by patient and disease characteristics. In general, these factors help stratify patients into low-, intermediate-, and high-risk categories. The evidence review focused on guidelines, meta-analyses, and phase III clinical studies evaluating the impact of adjuvant systemic therapies on disease-free and/or overall survival rates; a systematic review specifically on

patient and disease stratification factors was not performed. The recommendations for risk stratification were created by:

- Extraction of information from clinical practice guidelines found by our systematic review.
- Assessment of patient and disease factors evaluated or addressed in clinical trials included in our systematic review.
- Initial expert consensus on additional relevant factors that may not have been specifically addressed in the reviewed guidelines and clinical trials.

Recommendation 1

The following disease characteristics (histopathological parameters) are considered relevant (either prognostic or predictive) when making a decision regarding adjuvant systemic therapies for breast cancer:

- Lymph node status
- T stage
- Estrogen receptor (ER) status
- Progesterone receptor (PR) status
- Human epidermal growth factor receptor 2 (HER2) status
- Tumor grade
- Presence of tumor lymphovascular invasion (LVI)

Recommendation 2

The following risk stratification tools may be used in determining the utility of certain systemic therapies in patients with early-stage breast cancer:

- Oncotype DX score (for hormone receptor positive [HR+], node negative [N0] or $N1_{mic}$ or isolated tumor cells [ITC], and HER2 negative cancers)
- Adjuvant! Online (www.adjuvantonline.com)

Recommendation 3

The following patient factors should be considered in making adjuvant systemic therapy decisions:

- Age
- Menopausal status
- Medical comorbidities (including validated tools used to measure health status)

Recommendation 4

In those patients in whom chemotherapy would likely be tolerated and is acceptable to the patient, adjuvant chemotherapy should be considered for patients with the following tumor characteristics (in no particular order):

- Lymph node positive: one or more lymph nodes with a macro-metastatic deposit (>2 mm)
- ER− with T size >5mm
- HER2+ tumors
- High-risk lymph node negative tumors with T size >5 mm and another high-risk feature (see next recommendation)
- Adjuvant! Online 10-year risk of death from breast cancer >10%

Recommendation 5

When considering lymph node negative tumors with T >5mm, the following should be considered high-risk features (thus considered candidates for chemotherapy):

- Grade 3
- Triple negative (ER-, PR-, and HER2-)
- LVI positive
- An Oncotype DX recurrence score (RS) that is associated with an estimated distant relapse risk of 15% or more at 10 years
- HER2+

Recommendation 6

Patients with the following disease characteristics may not benefit from adjuvant chemotherapy: T <5 mm, lymph node negative and no other high-risk features (see Recommendation 5)

Recommendation 7

Adjuvant chemotherapy may not be required in patients with HER2-, strongly ER+ and PR+ breast cancer with any of the following additional characteristics:

- Lymph node positive with micrometastasis (<2 mm) only, *or*
- T <5mm, *or*
- An Oncotype DX RS with an estimated distant relapse risk of less than 15% at 10 years

Recommendations 8-14. Selection of Optimal Adjuvant Chemotherapy Regimens

Recommendation 8

In patients who can tolerate it, using an anthracycline-taxane containing regimen is considered the optimal strategy for adjuvant chemotherapy, particularly in those patients deemed to be high risk.

Recommendation 9

For patients in whom a taxane is contraindicated, an optimal-dose anthracycline regimen (doxorubicin ≥240 mg/m^2 or epirubicin ≥360 mg/m^2) is recommended.

Recommendation 10

The addition of gemcitabine or capecitabine to an anthracycline-taxane regimen is not recommended for adjuvant chemotherapy.

Recommendation 11

In patients older than 65 years, capecitabine is not recommended as an adjuvant chemotherapy option in lieu of adjuvant doxorubicin (Adriamycin) + cyclophosphamide (AC) or cyclophosphamide + methotrexate + 5-fluorouracil (CMF) (oral cyclophosphamide).

Recommendation 12

CMF (with oral cyclophosphamide) is an acceptable chemotherapy regimen for patients in whom an anthracycline and taxane is contraindicated.

Recommendation 13

The following adjuvant chemotherapy regimens can be used for patients with early-stage breast cancer (also see Recommendation 14 for non-anthracycline regimens):

- 5-fluorouracil + epirubicin + cyclophosphamide (all intravenous [IV]) (FEC)x3 → docetaxel (Taxotere [T])x3 (superior to FEC ×6)
- AC×4 → T×4 (superior to AC×4)
- Docetaxel (Taxotere) + doxorubicin (Adriamycin) + cyclophosphamide (TAC)×6 (superior to FAC×6)
- AC×4 → paclitaxel (P) administered weekly
- Dose-dense, dose-intense epirubicin + cyclophosphamide (EC) → P
- Dose-dense AC→ P (every 2 weeks)

Recommendation 14

TC (docetaxel/cyclophosphamide) is an adjuvant regimen that can be used when an anthracycline is not preferred.

Recommendations 15-25. Adjuvant Endocrine Therapy

Recommendation 15

For the purpose of selecting adjuvant endocrine therapy, the most reliable definitions of menopause are:

- Bilateral oophorectomy
- At least 12 months of amenorrhea prior to initiation of chemotherapy or tamoxifen
- In female patients age ≤60 years who experience amenorrhea secondary to chemotherapy or tamoxifen, defining menopause is difficult and

care must be taken when initiating an aromatase inhibitor (AI)

Recommendation 16

Adjuvant endocrine therapy should be considered in all patients with ER+ cancer, defined by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines as ER immunohistochemistry (IHC) staining ≥1%, taking into consideration overall disease risk, patient preference, and potential adverse effects.

Recommendation 17

Consensus was not reached on whether to administer adjuvant endocrine therapy in patients with ER- but PR+ tumors. See Section 3 in the original guideline document for details.

Recommendation 18

Tamoxifen for five years has been the standard of care, but tamoxifen for up to ten years is a reasonable option for premenopausal patients with ER+ tumors, regardless of chemotherapy use.

Recommendation 19

Ovarian ablation or suppression is a reasonable treatment option for premenopausal patients with ER+ tumors who refuse or are not candidates for any other systemic therapy.

Recommendation 20

In premenopausal patients with ER+ tumors (treated with or without chemotherapy) the addition of ovarian ablation or suppression to tamoxifen is not the standard of care.

Recommendation 21

In premenopausal patients with ER+ tumors, treated with or without chemotherapy, ovarian ablation or suppression plus five years of an aromatase inhibitor (AI) is not the standard of care.

Recommendation 22

The optimal* adjuvant endocrine therapy for postmenopausal patients with ER+ tumors should include an AI.

*Some consensus panel participants felt that the word "optimal" may not apply to all patients. The risk to benefit ratio of using tamoxifen vs AIs must be taken into account, recognizing the different side-effect profile of these medications.

Recommendation 23

Tamoxifen for up to ten years is an acceptable treatment for postmenopausal patients with ER+ tumors treated with or without chemotherapy.

Recommendation 24

For postmenopausal patients with ER+ breast cancer (treated with or without chemotherapy) the following are acceptable strategies for use of AIs:

- Upfront for five years (instead of tamoxifen)
- As a switch after two to three years of tamoxifen (for a total of five years of endocrine therapy)
- As extended adjuvant therapy for five years, after completing five years of tamoxifen

Recommendation 25

In patients with ER+ tumors who do not receive adjuvant endocrine therapy immediately after surgery or chemotherapy, delayed endocrine therapy is still clinically beneficial.

Recommendations 26-34. Adjuvant Targeted Therapy (HER2+ cancers)

Recommendation 26

Only patients with HER2+ breast cancer (IHC 3+, in situ hybridization (ISH) ratio ≥2, or 6+ HER2 gene copies per cell nucleus) should be offered adjuvant trastuzumab.

Recommendation 27

Trastuzumab plus chemotherapy is recommended for all patients with HER2+ node positive breast cancer and for patients with for HER2+ node negative breast cancer greater than 1 cm in size.

Recommendation 28

Trastuzumab therapy can be considered in small (≤1 cm) tumors as part of clinical studies or evidence-building programs (such as the one currently available in Ontario).

Recommendation 29

Trastuzumab can be administered with any acceptable adjuvant chemotherapy regimen.

Recommendation 30

The administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is generally not recommended because of the potential of increased cardiotoxicity.

Recommendation 31

Adjuvant trastuzumab can be initiated either concurrently or sequentially with the taxane portion of a chemotherapy regimen.

Recommendation 32

TCH (docetaxel/carboplatin/trastuzumab) is less cardiotoxic than AC→TH (doxorubicin/cyclophosphamide-docetaxel/trastuzumab) and is recommended for patients at higher risk for cardiotoxicity.

Recommendation 33

Phase III evidence for the addition of trastuzumab to some chemotherapy regimens such as TC (docetaxel/cyclophosphamide) does not exist. However, these regimens may be in use and are reasonable options, particularly to mitigate cardiotoxicity in certain patients.

Recommendation 34

Patients should be offered one year total of adjuvant trastuzumab, with regular cardiac functional assessments during this period.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Early-stage invasive breast cancer

Guideline Category

Evaluation

Risk Assessment

Treatment

Clinical Specialty

Oncology

Radiation Oncology

Surgery

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To create one guideline covering all systemic treatments for early breast cancer
- To create guidelines to ensure standardization of best practices

Target Population

Female patients who are being considered for or are receiving systemic therapy for early-stage invasive breast cancer

Interventions and Practices Considered

1. Assessment of relevant (either prognostic or predictive) disease characteristics (histopathological parameters)
2. Use of risk stratification tools (Oncotype DX score, Adjuvant! Online)
3. Consideration of patient factors (age, menopausal status, medical comorbidities)
4. Adjuvant chemotherapy with consideration of tumor and disease characteristics
5. Adjuvant chemotherapy regimens
    - Anthracycline-taxane containing regimens
    - Optimal-dose anthracycline regimen alone (if taxane is contraindicated)
    - Addition of gemcitabine or capecitabine to an anthracycline-taxane regimen (not recommended)
    - Capecitabine in patents older than 65 years (not recommended)
    - Cyclophosphamide + methotrexate + fluorouracil (CMF) with oral cyclophosphamide if anthracycline and taxane is contraindicated
    - TC (docetaxel/cyclophosphamide) if an anthracycline is not preferred
6. Adjuvant endocrine therapy
    - Consideration of menopause definition and patients with estrogen receptor (ER+) cancer
    - Tamoxifen
    - Ovarian ablation or suppression (only for patients who refuse or are not candidates for other systemic therapy)
    - Aromatase inhibitor
7. Adjuvant targeted therapy (for human epidermal growth factor receptor 2 positive [HER2+] cancers)
    - Adjuvant trastuzumab alone
    - Trastuzumab plus chemotherapy
    - Trastuzumab initiated concurrently/sequentially with the taxane component of chemotherapy but not with the anthracycline component
    - Cardiac functional assessments during adjuvant trastuzumab therapy

Major Outcomes Considered

- Breast cancer-free interval
- Breast cancer-free survival rate
- Bone mineral density
- Clinically complete response

- Overall survival rate
- Pathologically complete response
- Patient quality of life

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

A literature search on MEDLINE and EMBASE was conducted for the period from 2008 to March 5, 2012 and updated on May 12, 2014. The search was for articles on breast cancer plus systemic therapy (chemotherapy, hormonal/endocrine therapy, targeted agents, ovarian suppression/ablation), and was limited to randomized controlled trials (RCTs), guidelines, systematic reviews, and meta-analyses. Although in most cases chemotherapeutic agents were indexed to terms such as adjuvant therapy and the studies would be found by the index terms, we also included individual chemotherapy agents or regimens considered relevant to Ontario. The full search strategy is provided in Appendix C in the original guideline document. The Standards and Guidelines Evidence (SAGE) Directory of Cancer Guidelines (available at www.cancerview.ca) was searched in May 2012 for current versions of guidelines published in 2008 or later. Most guidelines listed were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and no further appraisal of quality was undertaken for the current guideline on systemic therapy in early breast cancer. National Institute for Health and Care Excellence (NICE) (UK), Scottish Intercollegiate Guidelines Network (SIGN) (UK), American Society of Clinical Oncology (ASCO) (US), National Comprehensive Cancer Network (NCCN) (US), National Health and Medical Research Council (Australia), and the New Zealand Guidelines Group sites were searched in February 2012 for guidelines not yet indexed in SAGE.

Study Selection Criteria

Clinical trials were included if they included at least 100 female patients with early-stage breast cancer randomized to at least one systemic agents and with survival rate (generally overall survival rate [OS] or disease-free survival rate [DFS]) as one of the primary or secondary outcomes to be determined according to the study design. Studies had to define the patient population as early or operable breast cancer, or provide a description in the abstract, methods, or results indicating that patients with early breast cancer were the main group studied. When tumor size and nodal status were reported, these were translated to stage according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 6th edition. Studies in which the title or abstract indicated the trial focused on metastatic breast cancer (other than locoregional lymph nodes), advanced, locally advanced breast cancer (LABC), non-invasive cancers (ductal carcinoma in situ [DCIS] or lobular carcinoma in situ [LCIS]), or treatment of recurrence were excluded. Because of overlap between early and LABC definitions, studies in which the patients were referred to as LABC but also indicated the distribution of stages were evaluated more carefully. Because Stages IIB and IIIA are also considered early in some definitions, these were included if Stage IIA was part of the patient population and at least one-half the patients had Stages I–IIB cancer. Studies with mostly Stage III–IV were excluded. Studies were excluded that focused on evaluation of supportive care such as drugs to prevent nausea and vomiting, gonadotropin-releasing agents to prevent ovarian damage, erythropoiesis-stimulating agents, or autologous hematopoietic stem-cell transplantation (AHST). Studies on bisphosphonates to prevent metastasis or cancer recurrence were included (with a final decision deferred to later in the process); studies to treat bone metastasis were excluded because they did not meet the definition of early breast cancer. A decision to include or exclude studies of granulocyte-colony stimulating factor (GCSF) to prevent or treat neutropenia was deferred to later in the guideline process; therefore, these were included in the initial screening.

Clinical practice guidelines were considered relevant if recommendations were based on a systematic review of the literature or were consensus-based with reference to the clinical evidence. When multiple versions of a guideline were located, only the most recent guideline was retained.

Additional Studies

Recent guidelines, systematic reviews, and meta-analyses were evaluated and the included studies were compared with those found in the literature search for this guideline. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published the fifth cycle meta-analysis at the end of 2011. It presented the latest update of individual patient meta-analysis for polychemotherapy based on RCTs worldwide and included data

available up to mid-2010. This gave extended follow-up and additional trials compared with the previous (fourth cycle) meta-analysis published in 2005. Because portions of the data included were comprehensive and current, these were used as a basis for some of the comparisons and the original studies were not obtained. In other areas, the current literature review revealed major new studies or extended follow-up of previous studies that needed to be considered along with the older publications. Therefore publications before 2008 referenced in the guidelines, reviews, or meta-analyses were obtained and compiled along with the newer data. For RCTs that were in progress, incomplete, or reported only as an abstract, additional targeted searches using MEDLINE, EMBASE, or Google were performed to find recent or complete reports where available.

See Section 2 in the original guideline document for more information on the literature search.

Number of Source Documents

Literature Search Results

The initial search in MEDLINE and EMBASE, after removal of duplicate citations, resulted in 7380 publications (6085 randomized controlled trials [RCTs], and 1295 systematic reviews and guidelines). After applying the inclusion/exclusion criteria in an initial screening (primarily by title and abstract), there were 253 articles representing 163 trials from the original search. A secondary screening of the titles by the Working Group reduced this to 216 articles; studies were eliminated if they were not relevant to Ontario (e.g., old drugs no longer used), duplicate publications, publications with exploratory analyses or correlations, and studies without survival rate endpoints. The literature search also resulted in 63 candidate clinical practice guidelines, of which 42 remained after discussion by the Working Group. Five of the guidelines by the Program in Evidence-Based Care (PEBC) and four others have been summarized or referred to in this evidentiary review. AGREE II ratings of the non-PEBC guidelines are provided in Appendix E in the original guideline document. Of the trials (RCTs) found in the literature search, 46 were trials that had not been included in the guidelines, meta-analyses, or systematic reviews discussed in the following subsections.

The literature search update of May 2014 resulted in 5350 RCT/trial publications and 1714 systematic reviews or guidelines. After screening, there were 110 publications of RCTs and 96 guidelines/systematic reviews/meta-analyses. The new guidelines and systematic reviews were not used unless updates of those already included in the current guideline. After adding in publications from other sources (reference lists, targeted searches for publications of studies initially found only as abstracts) there were 516 publications of trials.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Synthesizing the Evidence

Meta-analyses performed in other publications are cited but no meta-analysis was conducted in the preparation of this guideline.

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

The initial plan was to consolidate recommendations from Program in Evidence-Based Care (PEBC)/Cancer Care Ontario (CCO) guidelines on systemic therapy for female breast cancer according to pathology and menopausal status and to provide additional context and qualifying statements. After working on this approach, it was found that many relevant randomized controlled trials (RCTs) were not included in any of the guidelines under consideration, both because of topics covered and the dates of the literature searches. Updating all of the individual guidelines so they could be used in a summary guideline was considered unfeasible.

A different approach was used in which a literature search for recent publications was conducted. The starting point was selected to include studies or updates published after the literature searches in the PEBC guidelines and the National Institute for Health and Care Excellence (NICE) Guideline "Breast Cancer (Early and Locally Advanced): Diagnosis and Treatment". These guidelines, along with other guidelines or systematic reviews identified in the literature search, would be used as a source of publications for RCTs that were published before the literature search. This was not strictly an update of the previous guidelines as the research questions in the current guideline were not the same, because relevant issues have changed and because the current guideline was designed to be broader in scope. For topics in which a recent guideline, meta-analysis, or systematic review was found that covered most of the published trials, additional RCTs found in the literature search are listed so that the evidence base is complete, but they are not discussed unless they result in additional or different conclusions.

The evidence-based series (EBS) guidelines developed by the CCO/PEBC use the methods of the Practice Guidelines Development Cycle. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one member (GF) of the PEBC Early Breast Cancer Systemic Therapy Working Group, with input from the full group once initial screening was complete. The body of evidence in this review is primarily mature RCT data. The evidence forms the basis of the recommendations developed by the Early Breast Cancer Systemic Therapy Consensus Panel.

Formation of Guideline Development/Working Group

The Breast Cancer Disease Site Group (DSG) asked the PEBC to develop a guideline on Systemic Therapy for Early Female Breast Cancer. In consultation with the DSG, a Working Group was identified from the DSG membership. This Working Group consisted of six medical oncologists and one methodologist. The Early Breast Cancer Systemic Therapy Consensus Panel (see Consensus section and Appendix A in the original guideline document), consisting of medical oncologists selected to represent all regions of Ontario, reviewed the evidence base and initial draft recommendations, and voted on the final recommendations. The members of the consensus panel also reviewed the draft document at the same time as the Report Approval Panel (RAP) review.

A consensus panel process was used due to the large amount of evidence and wide scope of the document, the current use of several chemotherapy regimens that do not have direct RCT comparisons and that may have differential benefits in specific subpopulations of patients, possible differences in practice patterns among different centers and regions of Ontario, and to identify gaps in evidence for certain practices. The consensus process was envisioned as a way to standardize practice, to raise awareness of some of the issues surrounding treatment decisions, and to reveal practices that are not according to best evidence.

Research Question

What is the optimal adjuvant systemic therapy for female patients with early-stage operable breast cancer, when patient and disease factors are considered?

Initial Statements/Recommendations

Using the evidentiary base in Section 2 in the original guideline document, the Working Group developed a set of initial consensus statements or recommendations. These initial recommendations were developed through a consideration of the aggregate evidence quality, the potential for bias in the evidence, and the likely benefits and harms. The initial recommendations were voted on by a consensus panel as described in the next subsection. The consensus panel was provided the evidence summary (see Section 2 in the original guideline document) and the initial recommendations, but not the key evidence summaries or comments that appear following each recommendation in Section 1 in the original guideline document. Both initial and revised recommendations are provided in Appendix B in the original guideline document. The exact wording of the final recommendations in Section 1 in the original guideline document differ from those in the Appendix B in the original guideline document because cross-referencing to tables in Section 2 or other evidence was removed from the recommendation boxes and placed with the qualifying statements and key evidence. In a few cases, the wording was edited for clarity but it is consistent with the intent of the recommendation as voted on.

Consensus Panel Process

During the project planning stage it was decided that final recommendations would be decided on by consensus at a meeting, with participants being medical oncologists practicing in Ontario. All medical oncologists currently serving as members of the Breast Cancer DSG were invited. Additional medical oncologists with an interest in breast cancer were invited to ensure representation from all Cancer Treatment Centers and regions of Ontario. The initial list of people to invite was prepared by the Working Group chair (MT) in consultation with the Head of Medical Oncology or the Head of the Cancer Centre. Invitees who declined to participate were asked if they could recommend another medical oncologist from their institution/center with an interest in breast cancer. The consensus panel members are listed in Appendix A in the original guideline document and included the medical oncologists in the Working Group plus the additional medical oncologists who agreed to participate.

The Working Group prepared 34 recommendation statements based on the evidence in the systematic review in Section 2 in the original guideline document. Because a systematic review was not conducted on patient and disease stratification factors, draft recommendations on these (Recommendations 1-7) were based on clinical practice guidelines, factors included or evaluated in clinical trials in the systematic review, and experience of the Working Group members.

A modified Delphi technique was used to try to reach consensus. The draft recommendations were circulated to all consensus group members and voted on before the consensus meeting using a 5-point scale (strongly disagree, disagree, undecided, agree, and strongly agree). Consensus was defined as at least 80% agreement (agree or strongly agree) and with no responses of strongly disagree. Voting on the initial set of recommendations was coordinated using Survey Monkey (a third-party website), which allowed anonymous voting and feedback. Of those people receiving the online survey, 19 of 20 responded. Recommendations without consensus from the initial questionnaire were presented at a consensus meeting on November 23, 2012 and voted on by 16 participants after rewording (if required) and discussion. Some of the recommendations that met consensus but also had some responses of "disagree" were reviewed but not voted on again. No additional discussion was held at the consensus meeting for statements attaining consensus and all responses being undecided, agree, or strongly agree.

Questionnaire and Results

The original questionnaire, statements added or modified at the consensus panel meeting, and a tabulation of responses are provided in Appendix B in the original guideline document. In the online survey, 24 recommendations achieved consensus, whereas 10 recommendations did not attain consensus in their entirety (some recommendations contained multiple statements voted on separately). Of these ten statements, participants were able to attain consensus for at least part (i.e., at least one sub-statement or clause) for nine. Eight of the consensus statements had attained consensus with some disagreement and were discussed at the meeting but were not voted on again. The discussion has been incorporated into the comments, key evidence, and qualifying statements in the original guideline document.

The Delphi Technique

Consensus methods are a means of resolving conflicting scientific data. A consensus statement is often developed after a consensus conference where a comprehensive analysis by a panel of experts is undertaken to resolve a scientific or medical issue. Quantitative methods, such as meta-analyses, provide statistical overviews of the results of clinical trials and attempt to resolve inconsistencies in published studies. Consensus methods are concerned with deriving quantitative estimates through qualitative approaches.

Features of consensus methods include:

- Anonymity — to avoid dominance by panel members
- Iteration — to allow individuals to change their opinions
- Controlled feedback — to demonstrate the distribution of the group's response
- Statistical group response — to express judgment using summary measures of the full group response (providing more information than just a consensus statement)

The Delphi technique is a well-established consensus technique in scientific and medical research. Through the use of sequential questionnaires and regular anonymous feedback, this technique allows for collection, grouping, sorting, and ranking of data through structured communication. The technique also allows for attaining consensus among a group of individuals without requiring face-to-face contact.

Questionnaires are distributed to participants and responses are summarized to develop additional questionnaires in an attempt to seek agreement, disagreement, and new insights from the same pool of participants. The process continues until no new opinions are raised.

A modified Delphi Technique was applied to this project through multiple phases:

- Phase 1 — An initial questionnaire was administered to a group of chosen specialists in Ontario.
- Phase 2 — The results of the initial questionnaire were summarized and were distributed at the consensus meeting. A brief presentation on some of the relevant issues was made by the Working Group. Following discussion the respondent group answered another questionnaire that only included the questions for which there had not been consensus before the meeting. Although some statements had achieved

consensus on some of the clauses and therefore did not strictly require revote on all the clauses, it was decided that any statement not reaching consensus in its entirety would be voted on again in full.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Internal Review

Almost all Program in Evidence-Based Care (PEBC) documents undergo internal review. For this document, the consensus panel reviewed the document as part of the consensus recommendations-development process. Internal review was conducted by the Report Approval Panel (RAP), and the Working Group was responsible for incorporating the feedback and required changes. RAP had to approve the document before it could be sent to External Review.

Report Approval Panel Review and Approval

The purpose of the RAP review is to ensure the methodological rigor and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. For each document, three RAP members review the document: the Director and two others. RAP members must not have had any involvement in the development of the guideline before Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with the Assistant Director of Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

The RAP reviewed this document during September to October 2013. The RAP approved the document on October 16, 2013. Key issues raised by the Report Approval Panel are summarized in the original guideline document.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the draft document with recommendations modified as noted under Internal Review was circulated to external review participants for review and feedback.

The revised document was circulated to Consensus Panel members at the time of external review, as well as following completion of the external review process.

Methods

Targeted Peer Review

During the guideline development process, five targeted peer reviewers from across Canada considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Several weeks before completion of the draft report, the nominees were contacted by

email and asked to serve as reviewers. Four reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on March 24, 2014. Follow-up reminders were sent at two weeks and at four weeks. The Working Group reviewed the results of the survey.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals who are the intended users of the guideline. Breast Disease Site Group (DSG) members not part of the Working Group or consensus panel, plus all other medical oncologists, surgical oncologists, and radiation oncologists in the PEBC database who had indicated breast cancer as an area of interest were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1 in the original guideline document) and the evidentiary base (Section 2 in the original guideline document). Participants were asked to rate the overall quality of the guideline (Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited. The notification email was sent on March 24, 2014. The consultation period ended on May 2, 2014. The Working Group reviewed the results of the survey.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized controlled trials (RCTs), meta-analyses, clinical guidelines, and systematic reviews.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Safe and effective use of systemic therapy for early female breast cancer
- Improved survival rates

Potential Harms

Adverse effects associated with adjuvant chemotherapy, endocrine therapy and targeted therapy. See the evidence tables in Section 2 in the original guideline document for adverse events found in specific studies.

Contraindications

Contraindications

- Aromatase inhibitor (AI) therapy is contraindicated in pre or perimenopausal patients except in clinical trials
- Contraindications to anthracycline therapy include risk factors for cardiac disease

Qualifying Statements

Qualifying Statements

- Several of the systemic therapies discussed in this guideline can be considered in the neoadjuvant setting. However, this guideline makes recommendations specifically for adjuvant therapy for the following reasons: a) there is significant variability within the patient population for whom neoadjuvant therapy may be considered (from early, operable breast cancer to locally advanced breast cancer, which may have

unique treatment needs), and b) the systematic review of the evidence focused on trials with disease-free survival (DFS) and overall survival (OS) as endpoints, and thus excluded several trials that used pathologically complete response (pCR) as a primary endpoint. Therefore, the recommendations represent only some of the data that may be relevant to neoadjuvant patients.

- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.
- See the original guideline document for qualifying statements related to each recommendation.

Implementation of the Guideline

Description of Implementation Strategy

As indicated in Section 2 in the original guideline document, the systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada and issues specific to other jurisdictions (including low- or middle-income countries) were not considered. The recommendations encompassed in this guideline are most applicable to the Ontario (and likely North American) oncology practice setting. Although the approval of drugs is under the auspices of Health Canada, funding for particular systemic therapy agents is handled provincially in Canada, and this may impact on the ability to receive public reimbursement for certain therapeutic agents in each province. Some treatments as recommended by this guideline are fairly resource-intensive (e.g., taxane chemotherapy and trastuzumab). As such, these treatments may only be sustainable in higher-income nations. One must consider the local practice setting, including resource constraints, when considering the implementation of systemic therapy recommendations. Guidelines by groups such as the Breast Health Global Initiative may help users of this guideline to better choose the most resource-appropriate systemic therapies for their unique practice setting.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Eisen A, Fletcher GG, Gandhi S, Mates M, Freedman OC, Dent SF, Trudeau ME, Members of the Early Breast Cancer Systemic Therapy

Consensus Panel. Optimal systemic therapy for early female breast cancer. Toronto (ON): Cancer Care Ontario (CCO); 2014 Sep 30. 232 p. (Program in Evidence-Based Care Evidence-Based Series; no. 1-21). [473 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Sep 30

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

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Guideline Committee

Optimal Systemic Therapy for Early Female Breast Cancer Working Group

Composition of Group That Authored the Guideline

Authors: Andrea Eisen, Glenn G. Fletcher, Sonal Gandhi, Mihaela Mates, Orit C. Freedman, Susan F. Dent, Maureen E. Trudeau, members of the Early Breast Cancer Systemic Therapy Consensus Panel*

*See Appendix A in the original guideline document for a full list of members.

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-Based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, Early Breast Cancer Systemic Therapy Consensus Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest.

MT had responsibility as Head of Medical Oncology for donations from Roche and Amgen to the cancer program and fellowship funding from Eisai, Roche, Novartis, and Amgen. MT received grants or research support from Astellas, Medivation, and Novartis. SD is a principal investigator for the Aphinity trial; has received a speaking honorarium from Hoffman La Roche, Amgen, and Novartis; travel support from Celgene and Roche; and unrestricted educational grants from Roche, Pfizer, GSK, and Amgen. AE received a grant from Genomic Health and was a National Cancer Institute of Canada (NCIC) principal investigator for the OlympiA trial. SG received consulting fees as an advisory board participant and speaker at education rounds for Novartis. The other guideline authors declared they had no potential conflicts.

For the Consensus Panel, 10 members declared they had no conflicts of interest, and 4 (YM, VG, PB, BD) declared conflicts as indicated in Appendix A in the original guideline document. The Report Approval Panel (RAP) reviewers declared they had no conflicts. Two of the targeted external reviewers declared no potential conflicts of interest. The third declared having been a principle investigator on four clinical trials and having managerial responsibility for an organization that received >$5000 funding from a company/corporation with a vested interest in an object of the study.

The COIs declared did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca.

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario (CCO) Web site for details on any new evidence that has emerged and implications to the guidelines.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Cancer Care Ontario (CCO) Web site.

Availability of Companion Documents

The following are available:

- Optimal systemic therapy for early female breast cancer. Summary. Toronto (ON): Cancer Care Ontario; 2014 Sep 30. 35 p. Electronic copies: Available from the Cancer Care Ontario (CCO) Web site.
- Program in Evidence-Based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Electronic copies: Available from the CCO Web site.

Patient Resources

None available

NGC Status

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